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19JUN03 0816376-1 002534
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Request for grant of a patent

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Cardiff Road
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1. Your reference 101116-1-GB 19 JUN 2003

2. Patent application number

(The Patent Office will fill in this part)

0314260.1

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AstraZeneca AB
SE-151 85 Sodertalje
Sweden

Patents ADP number (if you know it)

7822441003

If the applicant is a corporate body, give the country/state of its incorporation

Sweden

4. Title of the invention

THERAPEUTIC AGENTS

5. Name of your agent (if you have one)

Thomas Kerr MILLER

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

AstraZeneca UK Limited
Global Intellectual Property
Mereside, Alderley Park
Macclesfield,
Cheshire SK10 4TG

Patents ADP number (if you know it)

7822471002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form.
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Continuation sheets of this form

Description	9
Claim(s)	1
Abstract	1
Drawing(s)	2

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

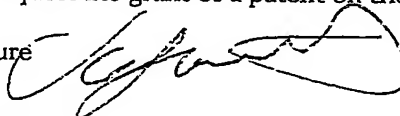
Request for substantive examination (Patents Form 10/77)

Any other documents
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11.

I/We request the grant of a patent on the basis of this application.

Signature



Date 16/06/03

12. Name and daytime telephone number of person to contact in the United Kingdom

Jennifer Bennett - 01625 230148

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Notes

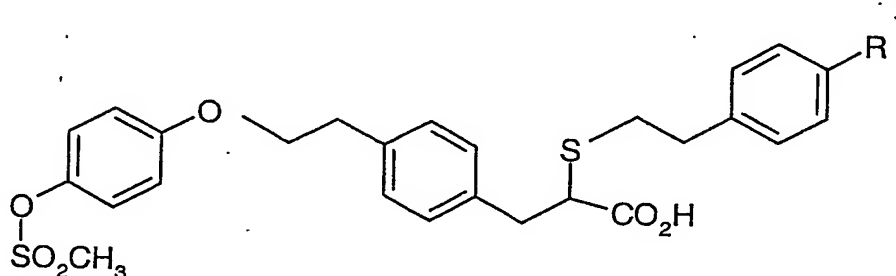
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Therapeutic AgentsField of the invention

The present invention relates to certain novel salts of 3-phenyl-2-arylalkylthiopropionic acid derivatives, to processes for preparing such compounds, to their utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome, to methods for their therapeutic use and to pharmaceutical compositions containing them.

10 Background of the invention

Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula B



B

15 wherein R¹ represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof which are selective PPAR α modulators. These compounds are useful in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome. The above compounds
20 contain a chiral centre. Often one enantiomer is much more active than the other and the preferred isomer is obtained by a resolution process or by chiral chromatography. By its nature a resolution process of a racemic mixture leads to 50% of the undesired material being discarded. The situation can be improved if the undesired enantiomer can be converted back into a racemic mixture by a racemisation process. Therefore there is a need for an efficient
25 and cost effective process for racemising the undesired isomer so that the resolution step can be repeated and reduce the material wastage in the process.

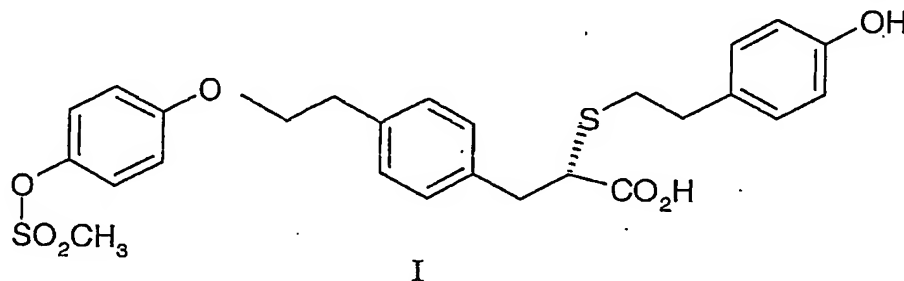
Description of the invention

The present invention provides a process for the preparation of substantially racemic 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid which comprises reacting 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent. Optionally the acid may be converted into an ester prior to racemisation or may be converted into an ester during the racemisation. Suitable esters include C₁₋₆ alkyl esters for example the methyl and ethyl ester. Suitable bases include potassium hydroxide or sodium hydroxide. Suitably the racemised ester is then hydrolysed to give the racemic acid for example by base hydrolysis.

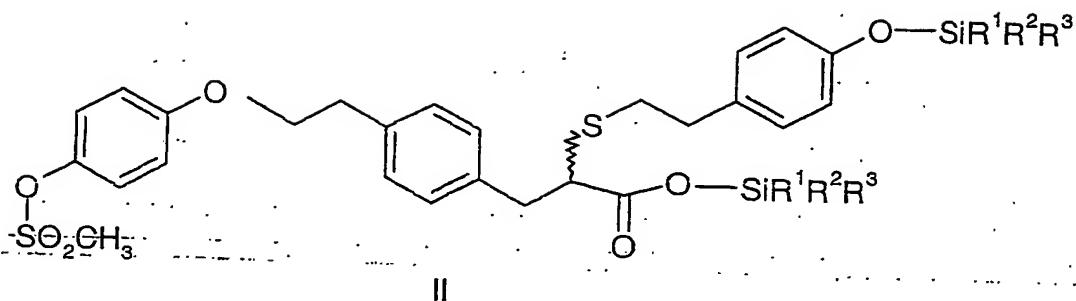
In one aspect the process comprises reacting 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a halosilane in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C.

The term enriched means that one enantiomer comprises >50 %, preferably between 60 and 80% and most preferably between 80 and 100% of the 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid in a mixture of the enantiomers of this acid.

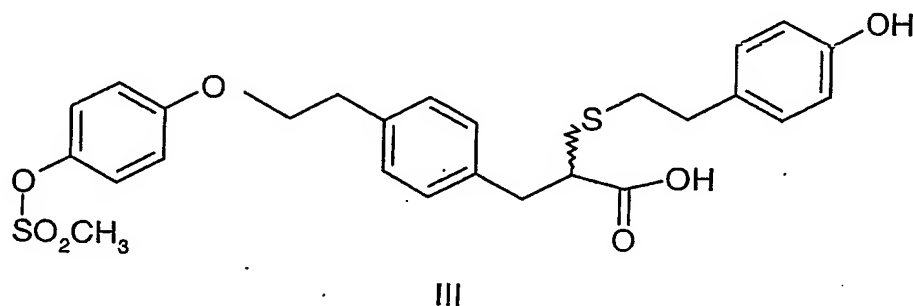
In another aspect the present invention comprises reacting a compound of formula I



with chlorosilane of formula ClSiR¹R²R³ in which R¹, R², and R³ independently represent a C₁₋₆ alkyl group or aryl in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula II



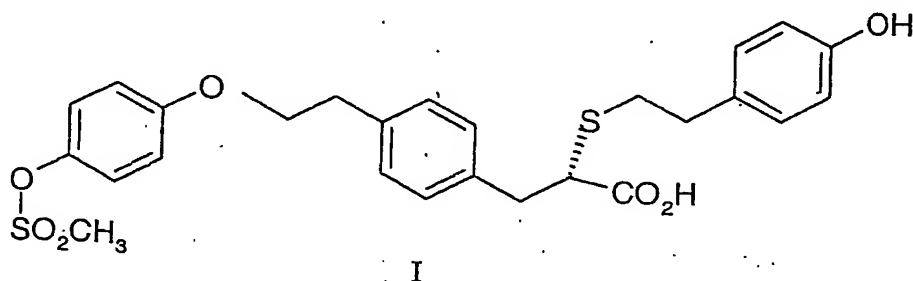
in which R^1 , R^2 , and R^3 are previously defined which is hydrolysed to give a racemic compound of formula III



Suitable nitrogenous bases include 1,8 diazabicyclo[5.4.0] undec-7-ene trialkylamines, optionally substituted pyridines and optionally substituted imidazoles. Particularly the base is 1,8 diazabicyclo[5.4.0] undec-7-ene.

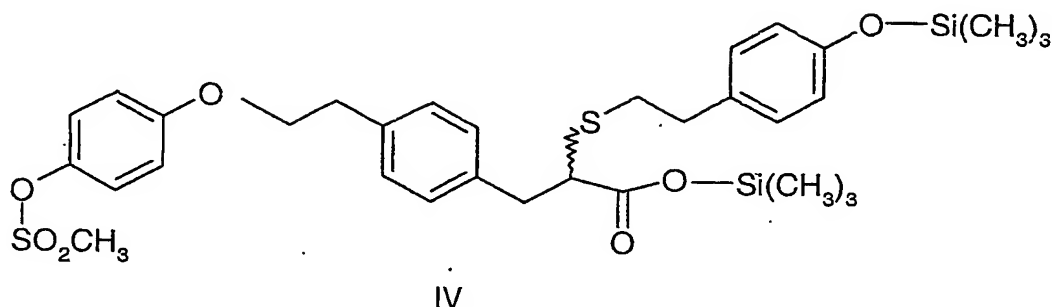
Suitable halosilanes include chlorotrialkyl silanes, for example chlorotriethylsilane and chlorodimethyl*tert*butylsilane and chlorotriarylsilanes for example chlorotriphenylsilane and mixed chloroarylalkyl silanes for example chlorodimethylphenyl silane. Particularly the chlorosilane is chlorotrimethylsilane.

In yet another aspect the present invention comprises reacting a compound of formula I

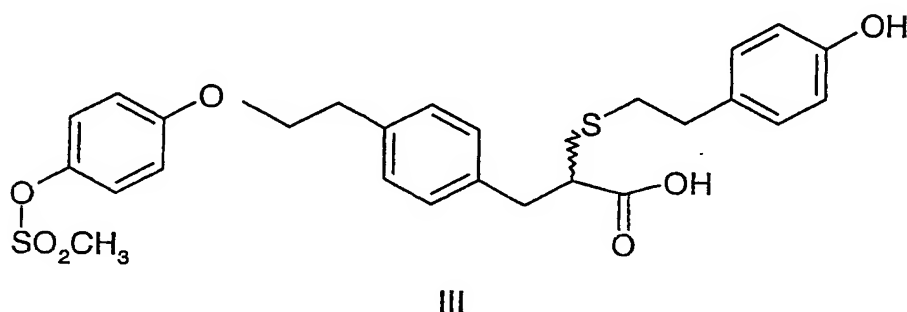


with chlorotrimethylsilane in the presence of 1,8 diazabicyclo[5.4.0] undec-7-ene

in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula IV



5 which is hydrolysed to give a racemic compound of formula III



The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

10

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product. Suitable solvents include ethers, for example dialkyl ethers, especially diC₁₋₆ alkyl ethers, or cyclic ethers for example tetrahydrofuran or hydrocarbons for example
15 toluene.

Preferably the enriched acid contains more of the (+) enantiomer (as measured in the conditions described below).

20 Examples

¹H NMR and ¹³C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ¹H frequencies of 300, 400, 500 and

600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Abbreviations

DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
DMF	<i>N,N</i> -dimethylformamide
10 THF	tetrahydrofuran
MeCN	acetonitrile
MeOH	methanol
TFA	trifluoroacetic acid
NH ₄ OAc	ammonium acetate
15 t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet
20 bs	broad singlet

Preparation of Starting Material

2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid

(i) Methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate

2-(4-Aminophenyl)ethanol (11g, 81mmol) and 32ml conc HCl was dissolved in acetone and cooled to 0°C. Sodium nitrite (5.6g, 81mmol) in 20ml water was added dropwise. The temperature was kept under 0°C. After one hour, methyl acrylate (70g, 808mmol) and CuI (1.6g, 8mmol) were added (<0°C). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and water was added. The water phase was extracted three times with EtOAc, the organic phases were pooled and washed with water, dried

(MgSO₄) and evaporated under reduced pressure. The crude product was purified by flash chromatography using a 65:35 mixture of EtOAc and heptane as eluent. Further purification by preparative HPLC (using a gradient of CH₃CN/ 5%CH₃CN-waterphase containing 0.1M NH₄OAc as eluent) gave 9.7g product (yield 49%) as an oil.

5 ¹HNMR (400MHz, CDCl₃): 2.84 (t, 3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

(ii) Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate

10 Triphenylphosphine (2.4g, 9mmol) was added to a solution of methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate (2.1g, 8.5mmol) and 4-(benzyloxy)phenol (1.7g, 8mmol) in 20ml toluene under nitrogen atmosphere. The solution was warmed to 55°C and diisopropyl azodicarboxylate (1.8g, 9mmol) was added. The reaction mixture was stirred at 55°C overnight.

15 The mixture was allowed to cool and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using a 80:20 mixture of heptane and EtOAc as eluent to yield 2.28g of the desired product (yield 61%) as colourless crystals.

¹HNMR (400MHz, CDCl₃): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29- 7.47 (m, 20 5H).

(iii) Methyl 2-chloro-3-{4-[2-(4-hydroxyphenoxy)ethyl]phenyl}propanoate

Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate (1.0g, 2.4mmol) and dimethyl sulfide (0.9g, 14mmol) was dissolved in 60ml CH₂Cl₂. Boron trifluoride etherate (2.0g, 14mmol) was added dropwise to the stirred solution. The reaction mixture was stirred for two days at room temperature. Another equivalent (0.4g, 2.87mmol) boron trifluoride etherate was added and the stirring was continued overnight.

Water was added. The phases were separated and the aqueous phase was extracted twice with 30 CH₂Cl₂. The organic phases were pooled, washed (water, brine), dried (Na₂SO₄) and evaporated under reduced pressure. Further purification by preparative HPLC using a gradient of CH₃CN/ 5% CH₃CN-waterphase containing 0.1M NH₄OAc gave 0.55g of the desired product (yield 52%) as an oil.

¹HNMR (400MHz, CDCl₃): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

(iv) Methyl 2-chloro-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate

Methyl 2-chloro-3-[4-[2-(4-hydroxyphenoxy)ethyl]phenyl]propanoate (334mg, 1.0mmol) and triethylamine (303mg, 3.0mmol) was dissolved in 20ml dichloromethane and cooled to -20°C under nitrogen atmosphere. Methanesulfonyl chloride (114mg, 1.0mmol) was added dropwise. The mixture was allowed to reach room temperature. After 2 hours dichloromethane was added, the mixture was washed (water, brine), dried (Na₂SO₄) and evaporated under reduced pressure to yield 394mg pure product (yield 96%).

¹HNMR (400MHz, CDCl₃): 3.02-3.11 (m, 5H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

(v) Methyl 2-({2-[4-(benzyloxy)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate

2-[4-(Benzyloxy)phenyl]ethanethiol (334mg, 1.4mmol), methyl 2-chloro-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate (394mg, 0.95mmol) and potassium carbonate (189mg, 1.4mmol) were dissolved in 14ml dry DMF and stirred under nitrogen atmosphere at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in toluene. The organic phase was washed (water, brine), dried (MgSO₄) and evaporated. Further purification by preparative HPLC using a gradient of CH₃CN/5% CH₃CN-waterphase containing 0.1M NH₄OAc gave 477mg of the desired product (yield 75%).

¹HNMR (400MHz, CDCl₃): 2.76-2.89 (m, 4H), 2.95 (dd, 1H), 3.09 (m, 5H), 3.20 (dd, 1H), 3.53 (m, 1H), 3.70 (s, 3H), 4.15 (t, 2H), 5.06 (s, 2H), 6.91 (m, 4H), 7.07-7.24 (m, 8H), 7.31-7.48 (m, 5H).

(vi) Methyl 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate

To a solution of methyl 2-([2-(4-(benzyloxy)phenyl)ethyl]thio)-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate (477mg, 0.8mmol) and 15ml dichloromethane, dimethyl sulfide (239mg, 3.8mmol) and boron trifluoride etherate (545mg, 3.8mmol) were added. After 18 hours of stirring water was added to the reaction. The phases were separated and the aqueous phase was extracted twice with dichloromethane. The organic phases were pooled, dried (MgSO₄) and evaporated under reduced pressure.

274mg of the desired product (yield 67%) was obtained as an oil.

¹HNMR (400MHz, CDCl₃): 2.70-2.85 (m, 4H), 2.91 (dd, 1H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 4.13 (t, 2H), 6.72 (d, 2H), 6.87 (d, 2H), 6.99 (d, 2H), 7.10-7.22 (m, 6H)

(vii) 2-([2-(4-Hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid

Methyl 2-([2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate (105mg, 0.2mmol) was dissolved in 6.5ml of a 7:1 mixture of THF and water and cooled on an ice-bath. Lithium hydroxide (9.4mg, 0.4mmol) was added. Water was added to the reaction mixture after 24 hours of stirring at room temperature. The THF was evaporated under reduced pressure and the residue was acidified with 1M hydrochloric acid. The water phase was extracted with EtOAc (x3), the organic phases were pooled, washed (water, brine), dried (MgSO₄) and evaporated. The crude product was purified using preparative HPLC (eluent: CH₃CN / 5% CH₃CN-waterphase containing 0.1M NH₄OAc) to give 74mg of the desired product (yield 97%) as an oil.

¹HNMR (400MHz, CDCl₃): 2.68-2.95 (m, 5H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.47 (m, 1H), 4.12 (t, 2H), 6.70 (d, 2H), 6.86 (d, 2H), 6.97 (d, 2H), 7.12-7.21 (m, 6H).

¹³CNMR (100MHz, CDCl₃): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

(viii) (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid

The racemate of 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)-oxy]phenoxy}ethyl)phenyl]propanoic acid was separated into its enantiomers using chiral chromatography: A-Chiralpak-AD JDB01+ AS003 (336 x 100 mm i.d.) and ethanol/formic acid 100/0.01% was used as mobile phase. The racemate (9 g) was dissolved in ethanol and injected onto the column. The first eluting peak was collected and UV-detected. The product (4.1 g) was obtained with an enantiomeric purity >99%. The optical rotation was found to be $[\alpha]_D^{20} = -33^\circ$ by dissolving the enantiomer in methanol to give a concentration of 0.64 g/100ml. The optical rotation was measured at 20 °C using the sodium line at 589 nm. The (+) enantiomer is isolated subsequently from the column and is used as a starting material for the racemisation reaction.

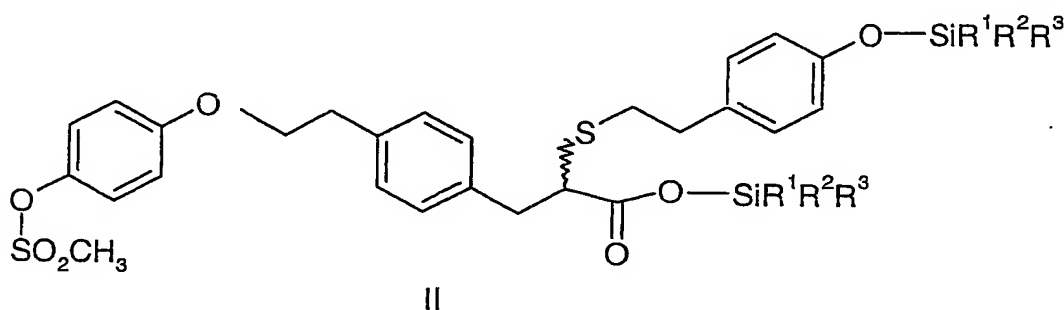
^1H NMR (500 MHz, CD_3OD): 7.17-7.22 (6H, m), 6.99 (2H, d), 6.94 (2H, d), 6.69 (2H, d), 4.17 (2H, t), 3.46 (1H, t), 3.16 (3H, s), 3.13 (1H, dd), 3.05 (2H, t), 2.69-2.88 (5H, m).

Example 1

1,8 Diazabicyclo[5.4.0] undec-7-ene (DBU) (4.11g) was added by syringe over 5 minutes to a stirred mixture of (+)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid (3.83g), toluene (8.65g) and tetrahydrofuran (44g) followed by the addition of chlorotrimethylsilane (2.24g) by syringe over 5 minutes. The resultant slurry was stirred at room temperature until the reaction was complete (3 hours). 2N Hydrochloric acid (31.2g) was added to the reaction mixture to hydrolyse the TMS ester, followed by brine. After separation of the aqueous layer, further brine was added, and the pH was adjusted to pH 2.5-3.5 by the addition of 1M sodium bicarbonate solution. The aqueous layer was separated and the organic layer was distilled at atmospheric pressure to remove water. Ethanol is added and a vacuum distillation carried out to remove THF and give a solution of racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]-propanoic acid in ethanol.

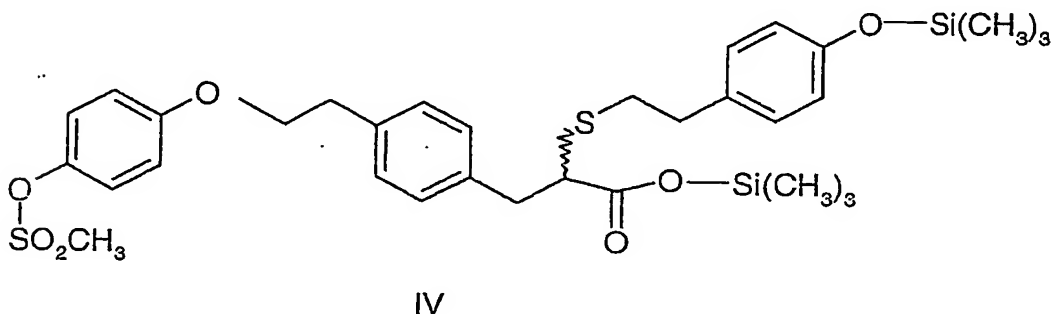
Claims:

1. A process for the preparation of substantially racemic 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid which comprises reacting 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent.
2. A process for the preparation of substantially racemic 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid which comprises reacting 2-{{2-(4-hydroxyphenyl)ethyl}thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with chlorotrimethylsilane in the presence of 1,8 diazabicyclo[5.4.0] undec-7-ene in the presence of an inert solvent at a temperature in the range of 0 to 150°C.
3. A compound of formula II



R^1 , R^2 , and R^3 independently represent a C_{1-6} alkyl group or aryl.

4. A compound of formula IV



ABSTRACT**Title : Therapeutic Agents**

The present invention provides a process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-
10 propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent.

PCT/GB2004/002599

